

Determining the Adequacy of Existing Data

1.0 Introduction

The EPA's High Production Volume Challenge Program ("Challenge Program") is an important and necessary step towards gathering basic hazard information on those chemicals manufactured, and thus presumably used, at high volumes throughout the United States, and make this information publicly available. In order to implement this program, two important parameters need to be identified: 1) a minimum data set to initially characterize the hazard of a high production volume (HPV) chemical; and 2) criteria and/or guidance for determining whether existing data meet the requirements set forth in (1).

The EPA is fortunate to be able to use the experience of a similar activity that has been ongoing at the international level since 1990, the Organization for Economic Cooperation and Development's (OECD) program known as the Screening Information Data Set (SIDS) program, to identify the minimal data set that provides a basic knowledge of the hazards of an HPV chemical.

The Challenge Program has adopted SIDS as the minimum data set to initially characterize the hazards of an HPV chemical. The Challenge Program is similar in substance, but distinct in process, from the OECD SIDS program. However, it is anticipated that the Challenge Program will benefit from the experience and judgment of the OECD SIDS process and can serve as a source for US contributions to the OECD effort.

The second parameter, developing guidance for determining the adequacy of existing data in meeting a minimum standard of acceptability, is the focus of this document.

2.0 Purpose

There are approximately 2,800 chemicals¹ on the current U.S. EPA list of HPV chemicals (available at: <http://www.epa.gov/opptintr/chemtest/hpv.htm>). The purpose of the Challenge Program is to develop a minimum set of hazard information on each of these chemicals. This hazard information can either be existing data or data that need to be generated. An evaluation of the existing data on each chemical is necessary to determine whether additional testing is required.

¹ This figure represents the HPVs subject to the Challenge Program. The total number of HPVs, approximately 3,000 chemicals, has been pared down by eliminating polymers and inorganics.

The purpose of this guidance document is to provide guidance for accepting or rejecting data used to describe the basic hazard (as characterized by data from the SIDS base set) of a chemical. The guidance is offered primarily for the entity submitting the data (“sponsor”), but will likely also be useful to the EPA and other reviewers. Adherence to this guidance is also likely to result in international acceptance of data under the OECD SIDS program.

3.0 The SIDS Data Elements: Screening Tools

Appendix A contains a list of the tests included in the SIDS. *The SIDS represents a minimum data set and thus should only be used for initial or screening level hazard assessments.* SIDS information may be used to make judgments on potential hazard, and to help determine what kinds of further information may be necessary to refine those judgments.

For example, the physical/chemical data provide information on the physical form and likely environmental medium in which the chemical will reside. This is important in order to determine the likely route of exposure to humans and ecological receptors. The environmental fate and pathway data are important for determining where a chemical may ultimately reside and how long it might stay there. Ecotoxicity and health effects data are critical elements of hazard assessments (toxicity endpoints of interest and qualitative route/dose information) and are important for guiding further testing to refine dose-response relationships that might be useful in future assessment activities.

Each endpoint in Appendix A is an important piece of information regarding the potential hazard of a chemical. Ideally, tests to gather such information would be conducted under optimum conditions; hence, the use of OECD and other equivalent test guidelines for the SIDS. However, it is important to consider existing information that might not have been generated under ideal conditions for the purpose of meeting a specific SIDS data element².

4.0 Tiered Evaluation of Sponsor Data Package

The Challenge Program will involve the **gathering and evaluation** of available data and a proposed testing plan by an HPV chemical sponsor to fulfill the basic SIDS. Again, the purpose of the Challenge Program is to provide screening-level hazard information on all HPV chemicals manufactured or imported into the U.S. Therefore; it is not important whether this information

² If one can arrive at a conclusion about a specific effect from an “old” study, or by inference from other information (weight of the evidence analysis), it might not be necessary to do further testing for that specific effect.

comes from existing data or newly conducted studies - as long as the information is judged adequate and is available for review by the general public.

In Tier I, existing data will be subjected to a minimal criteria list to assess overall scientific integrity of the information. It is presumed that existing data which followed OECD (or equivalent) guidelines will be considered directly in Tier II. Any data or information which do not meet these minimal criteria will be rejected for further consideration in the Challenge Program. In Tier II, a more rigorous evaluation of existing data that has passed Tier I will occur.

5.0 Tier I

Tier I is a screening process designed to allow only potentially useful information to move forward to Tier II in the assessment of existing data for the purposes of the Challenge Program.

The 1997 SIDS Manual (<http://www.epa.gov/opptintr/sids/sidsman.htm>) provides some guidance on how to assess existing data for the purpose of determining whether additional testing is needed to fulfill one or more of the SIDS data elements (Sections 3.4 and 3.5 of SIDS Manual, attached as Appendix B). Based on this information, along with EPA's experience in receiving and evaluating many different types of studies over the years, the following general criteria have been developed for determining whether existing information is worthy of further scrutiny in Tier II of the Data Adequacy process:

Minimal scientific/experimental/reporting requirements. Each submitted test plan must contain a "robust summary"³ which includes an objective, discussion of methods, and results for each endpoint for which testing is not proposed. The following minimal requirements need to be met, and if one or more are not met, that data will not advance to Tier II and that particular endpoint will be identified as a data gap that needs to be filled with testing under the Challenge Program (NOTE: There are specific test guidelines for each study in the basic SIDS; the reader is referred to each guideline for additional, study-specific information on minimum requirements - see **Appendix A**):

5.1 Required for all SIDS endpoints:

A. Test Substance Identification. Adequate description of test substance, including chemical purity and identification of impurities.

³ Guidance on the content and format of a robust summary is under development. Full study reports will be made available to EPA upon request.

5.2 Required for Physicochemical endpoints:

- A. Temperature (for vapor pressure and water solubility values).

5.3 Required for Environmental Fate Endpoints:

- A. Temperature. Must be recorded and reported for all endpoints/estimations.
- B. Controls. Appropriate controls must be used and reported.
- C. Statistical Analysis. Statistical analyses must be performed and presented with all tests.

5.4 Required for Ecotoxicity and Human Health Effect Endpoints:

- A. Number of Organisms. The number of organisms in each dose/concentration group must be reported. If appropriate (i.e., for mammalian studies but not ecotoxicity studies), the number per sex must be recorded.
- B. Dose/Concentration Levels. The number and amount of each dose/concentration used in the experiment must be reported.
- C. Route/Type of Exposure. The route/type of exposure (e.g., oral, inhalation, etc. for mammalian studies and static, flow-through, etc. for ecotoxicity) used must be reported.
- D. Duration of Exposure. Duration of exposure must be reported. The time will change by endpoint/study type (see Appendix A).
- E. Species. The species (and strain if appropriate) must be reported.
- F. Controls. All studies must have negative controls, and some studies (biodegradation, *Salmonella*/Ames assay) must also have positive controls. If a vehicle is used in administration of test agent, the presence of a vehicle control should be reported. Possible exceptions would be allowed for acute mammalian toxicity studies.
- G. Statistical Analysis. Statistical analyses must be performed and presented with all tests, with some exceptions (e.g., the *Salmonella*/Ames assays).

6.0 Tier II

A process to review the adequacy of data that have passed through Tier I requires a more rigorous analysis. The SIDS data elements listed in Appendix A consist of different study/estimation methods that can be grouped under four categories (physical/chemical properties, environmental fate and pathways, ecotoxicity tests, and health effects tests). Each of the studies included in the SIDS is unique in what it assesses and in terms of cost, time, and sophistication; therefore, determination of data adequacy will be done at the individual study level although the presence of multiple studies on a given endpoint may be relevant to the judgment.

Guidance is provided below for each of the SIDS study types/estimation methods in terms of the information that is necessary to give credence to a study. For the most part, the issues discussed suggest accepting data generated under old or not widely used protocols. For reference purposes only, the applicable OECD guidelines are provided. *The use of sound scientific judgment is the most important principle to follow* in evaluating data to determine whether it is adequate for the purposes of meeting a given data requirement. For example, there may be several repeated dose studies available on a particular chemical, none of which would be acceptable due to some deficiency (i.e., low number of test animals/dose group, only one dose group in addition to control group, change in dose amount or frequency during the course of the study, etc.). Collectively, however, the different studies show effects in the same target organ at approximately the same dose and time frame. This could satisfy the repeated dose toxicity data element.

This is not an endorsement for initiating studies using other than currently approved OECD (or other equivalent) guidelines for eventual submission under either the U.S. Voluntary Testing Program or the OECD SIDS program. Rather, it is an attempt to use available data for the purpose of hazard screening. All newly conducted testing will be done using current test guidelines.

6.1 Physical/Chemical Property Tests⁴

Information under this category is important for describing the physical state and basic chemical properties of an HPV chemical. For all the physical/chemical data discussed below, submitted information in the form of quantitative values may be considered acceptable if taken from reliable references (e.g., CRC Handbook of Chemistry, Merck Index) in lieu of an actual study. In all cases, however, the following information must be included in a data submission: temperature, barometric pressure, and detailed description of method used (even if taken from a handbook).

⁴ Some information is taken from Appendix B (Sections 3.4 and 3.5 of the OECD SIDS Manual). Additional information is also available in the same appendix.

Melting point and boiling point (OECD Guidelines 102 and 103, respectively). It may not be necessary to measure melting point for liquids with estimated melting points of less than 0°C, or to measure boiling points for liquids with estimated boiling points of greater than 300°C.

Vapor pressure (OECD Guideline 104). Calculations showing a value of $<1 \times 10^{-5}$ Kpa at 25°C may be acceptable to preclude measuring vapor pressure.

Octanol/water partition coefficient (OECD Guidelines 107 and 116). Calculated or estimated values are encouraged, however, if the estimate is greater than 6 (for a log K_{ow}), it may not be considered reliable.

Water solubility (OECD Guidelines 105). Quantitative values are needed; qualitative descriptions (e.g., very soluble, insoluble) are not acceptable.

6.2 Environmental Fate and Pathway Tests⁴

Obtaining information on environmental fate (both in terms of time and space) and environmental pathway (distribution in environmental media) are important in determining environmental behavior and routes of exposure.

Photodegradation (OECD Guideline 113). Estimation methods may be acceptable.

Stability in water (OECD Guideline 111) Estimation methods may be acceptable.

Biodegradation (OECD Guidelines 301a-f, 302a-c). The following information is needed from any ready biodegradability test: the number of microorganisms; how long it takes for 10% degradation; and the total degradation at the end of the test.

Transport and distribution. Given the data collected on photodegradation, stability in water, and biodegradation, sponsors are encouraged to evaluate this information to predict environmental distribution and fate (i.e., half-life determination). The OECD program advocates the use of computer modeling techniques such as FUGMOD (a fugacity-based model) to estimate the partitioning and distribution of a chemical in the environment.

6.3 Ecotoxicity Tests⁴

Traditionally, SIDS ecotoxicity data have focused on characterizing hazards in the aquatic environment. Toxicity to terrestrial organisms, while not part of the basic SIDS test, may be

required based on the physicochemical properties and environmental fate/pathway tests/estimations, and the potential use of the HPV chemical of concern.

Acute/prolonged toxicity to fish (OECD Guidelines 203, 204); Acute toxicity to aquatic invertebrates (OECD Guidelines 202); and Toxicity to aquatic plants (OECD Guidelines 201). The U.S. EPA requires the following information for all aquatic toxicity studies:

- test report (note deviations from method)
- test substance (describe analytical procedures)
- test procedures and conditions (standard/recognized procedures, acceptable test species, appropriate acclimation procedures followed, certain conditions noted [test temperature, dissolved oxygen levels, pH, lighting], and no position effects due to placement of test units)
- test medium and dilution water (correctly made, specified hardness and salinity range, all contaminants reported, acceptable levels of particulates, total organic carbon, chemical oxygen demand, un-ionized ammonia, residual chlorine, pesticides, heavy metals, and PCBs)
- test concentrations/dose levels (measured concentrations preferred over nominal concentrations, replication adequate, concentrations maintained during test)
- controls (number adequate, upper limit on mortality not exceeded, response acceptable)
- test endpoints and reported data (data quality assured and good laboratory practices followed)
- statistical analyses (correct tests or procedures used [e.g., parametric or non-parametric] to determine if there is difference between treated or controls)

6.4 Health Effects Tests

The series of studies discussed below represent a variety of endpoints (general systemic toxicity under acute and repeated dose exposure scenarios, genetic toxicity, reproductive toxicity, and developmental toxicity) that represent a reasonable starting point to identify the potential hazards of a chemical.

In general, the following information should be included in all study summaries: descriptions of test species, their acclimation, care, handling and health, diet and feeding schedule, test concentrations and dose levels, test end-points evaluated and reportable data/procedures.

Some of these requirements are not relevant for some assays, e.g., genetic toxicology studies using cell cultures, and in some cases additional requirements such as culture conditions should be included.

Acute toxicity. (OECD Guidelines 401-403). The following endpoints are of interest in acute toxicity studies: lethality, tolerance, and qualitative information on potential target organs. Key parameters are the number of animals/dose (usually 5), the number of dose levels or concentrations (usually >2), and the number of days of observation (14) following the single dose (or multiple doses over a 24-hour period). If no mortality is observed at dose levels of 2000 mg/kg (oral and dermal) or 5 mg/L, or the maximum attainable air concentration given the physicochemical properties of the test agent (inhalation), then no testing is required and the LD₅₀/LC₅₀ is reported as greater than the dose level used.

Estimation of lethality (an LD₅₀ or an LC₅₀) from less than perfect data may be more palatable than conducting another test. For example, the use of 2-3 animals (same sex)/dose, or 7-14 days of observation may be acceptable assuming there are no residual health effects for several consecutive days prior to study termination. This information would be enhanced by repeated dose toxicity data that supports the estimation/data for not conducting additional acute toxicity studies.

Genetic Toxicity (in vitro and in vivo)⁵. Genetic toxicity testing provide data useful in assessing the potential of chemicals to cause mutations, which are implicated in the induction of carcinogenicity, heritable mutagenicity, cellular aging, etc. Also, the two major endpoints in genetic toxicity should be addressed by the testing, i.e., gene mutation and chromosome mutation. This is achieved by testing in the *Salmonella*/Ames assay and in one of the two somatic cell *in vivo* cytogenetics tests (micronucleus or chromosomal aberrations). Key parameters include the selection of dose levels, the number of cultures/dose or number of animals/dose (the latter usually 5), the number of doses (usually > 3), the number and timing of harvest/sacrifice times, the presence of activation systems, and the route of administration.

Genetic toxicity (in vitro). (OECD Guidelines 471-473, 476, 479-482). Bacterial (*Salmonella typhimurium* or *Escherichia coli*) or non-bacterial (lymphoma, CHO, etc.) gene mutation tests, and mammalian cell chromosomal studies (many different cell lines). All studies require positive and negative controls, and should be conducted with and without mammalian metabolic activation. Since certain

⁵ EPA policy requires in vivo testing when there are no in vitro data available.

chemical classes do not respond well to the *Salmonella* assay, they should be tested in other systems such as one of the nonbacterial gene mutation tests.

Genetic toxicity (in vivo). (OECD Guidelines 474-475, 477-478, 483-86). A variety of acceptable test organisms for assessing gene mutations (fruit fly) or chromosomal changes in structure or number (mouse, rat, hamster); all studies require positive and negative controls.

Repeated dose toxicity, reproductive toxicity, and developmental toxicity. The purpose of these studies is to provide information on : (1) potential target organs, severity of effect, tolerance, and possible reversibility of effects (repeated dose, general toxicity); (2) potential adverse effects on reproductive organs and function (reproductive toxicity test); and (3) potential adverse effects on the developing fetus (developmental toxicity screen). Taken together, studies which provide the information listed in Table 1 would be considered for acceptability in fulfilling these SIDS endpoints in the Challenge Program. Table 2 lists the various study design scenarios that would be considered acceptable.

Table 1: Required Information for Selected Mammalian Toxicity Endpoints		
General Toxicity	Reproductive Toxicity	Developmental Toxicity
1. Body weight/body weight changes. 2. Food and water consumption 3. General toxic response by sex and dose 4. Nature, severity and duration of clinical observations (whether reversible or not) 5. Clinical biochemistry and hematological tests, both with relevant base-line values 6. Time of death during the study or whether animals survived to termination 7. Body weight and organ weights at sacrifice 8. Necropsy findings 9. Detailed description of histopathological analysis	1. Effects on reproduction, fertility, gestation 2. Histopathological analysis of testes with special emphasis on the stages of spermatogenesis (NOTE: This is not necessary for reproductive toxicity screen in which males are dosed for 10 weeks prior to mating.) 3. Number of live births and post implantation losses 4. Number of implantations, corpora lutea, litter size, and litter weights at time of recording	1. Effects on offspring, postnatal growth (depending on protocol) 2. Number of pups with grossly visible abnormalities 3. Number of implantations, corpora lutea (recommended), litter size, and litter weights at time of recording

Table 2: Possible Study Designs to Meet Selected Mammalian Toxicity Endpoints			
Study Designs	General Toxicity	Reproductive Toxicity	Developmental Toxicity
28-day (such as OECD Guidelines 407, 410, or 412) or 90-day repeated dose studies	✓		
Combined repeated dose study and a developmental/reproductive toxicity screen (OECD Guideline 422)	✓	✓	✓
Reproductive toxicity test (OECD Guideline 415 or 416)		✓	✓
Developmental toxicity test (OECD Guideline 414)			✓
Reproductive/developmental toxicity screen test (OECD Guideline 421)		✓	✓

APPENDIX A

SCREENING INFORMATION DATA SET (SIDS)

SIDS Data Elements		
SIDS Category	Test/Estimation Endpoint	OECD Guideline (or equivalent)
Chemical and Physical Properties	Melting point	OECD 102
	Boiling point	OECD 103
	Vapor pressure	OECD 104
	Partition coefficient (log K _{ow})	OECD 107, 116
	Water solubility	OECD 105
Environmental Fate and Pathways	Photodegradation	OECD 113
	Stability in Water	OECD 111
	Biodegradation	OECD 301, 302
Ecotoxicity Tests	Acute toxicity to fish	OECD 203, 204
	Acute toxicity to aquatic invertebrates	OECD 202
	Toxicity to aquatic plants	OECD 201
	Chronic aquatic invertebrate test (When appropriate)	OECD 202
	Terrestrial toxicity test (When appropriate)	OECD 207, 208,
Human Health Effects	Acute Toxicity	OECD 401-403
	General Toxicity (repeated dose)	OECD 407-413, 422
	Genetic Toxicity (effects on the gene and chromosome)	OECD 471-486
	Reproductive Toxicity	OECD 415, 416, 421, 422
	Developmental Toxicity	OECD 414, 421, 422

APPENDIX B

Sections 3.4 and 3.5 of the OECD SIDS MANUAL